EXPRESS MAIL NO.: EV 262272503 US
DATED DEPOSITED: FEBRUARY 13, 2003

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#13
M.G.J
3/5/03

Applicant:	Weigel et al	Atty Dkt No:	3554.085
Serial No:	09/842,930	Examiner:	L. Spector
Filed:	April 25, 2001	Art Unit:	1647
For:	IDENTIFICATION AND USES OF A HYALURONAN RECEPTOR FOR ENDOCYTOSIS		

Box Fee Amendment
Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF PAUL H. WEIGEL, Ph.D. UNDER 37 C.F.R. § 1.132

Sir:

I, Paul H. Weigel, of lawful age declare:

1. I am an Applicant of the above-referenced patent application and a co-inventor of the invention claimed in the subject application.

2. I have reviewed the reference by Zhou et al., Journal of Biological Chemistry (1999) 274:33831, which was cited by the Examiner in the rejection under 35 USC § 102(a)/103(a) made in the Official Action mailed August 16, 2002 in the present application, and which lists Bin Zhou, Janet A. Oka, Anil Singh, and Paul H. Weigel as authors.

3. Janet A. Oka, who was listed as a co-author of the Zhou et al. reference, and Janet A. Weigel, who is listed as a co-inventor of the present invention as claimed in the subject application, are the same person, the "Oka" being Janet Weigel's maiden surname.

4. Anil Singh was listed as a co-author of the Zhou et al. reference but was not also included as an inventor of the present invention, as he was not a co-inventor of the invention described and claimed in the present patent application. This individual was a staff laboratory technician working under the direction and supervision of the inventors.

5. I have also reviewed the reference by Yannariello-Brown et al., Glycobiology (1997) 7:15-21, which was cited by the Examiner in the rejection under 35 USC § 102(b)/103(a) made in the Official Action mailed August 16, 2002 in the present application, and which lists Judith Yannariello-Brown, Bin Zhou, and Paul H. Weigel as authors. This reference describes preliminary work from my lab on the identification of a Hyaluronan Receptor from rat liver sinusoidal endothelial cells. Following the identification of an ~175 kDa protein having HA-binding activity from rat liver endothelial cells, as described in the Yannariello-Brown et al. reference, we diligently attempted to isolate and purify the mammalian HARE and identify the amino acid sequence thereof. However, this proved to not be a simple task, and more than three years passed after the submission of the Yannariello-Brown et al. reference until sufficient evidence

was available to accurately isolate and purify the 175 kDa purified mammalian HARE.

We worked diligently from about 1992-1997 to purify the liver HA receptor using classical biochemical purification techniques, such as those described in the above Yannariello-Brown et al. 1997 reference. Despite this effort, and our extensive protein purification experience, we were not successful. In fact, at one point we believed that we had achieved a high enough degree of purity to send a protein sample for N-terminal amino acid sequencing. To our disappointment the amino acid sequence we obtained (>15 residues) was a match for the mannose receptor, which is a membrane protein of similar size to that of the 175 kD HARE.

A further indication of the difficulty in purifying this liver HA receptor is evidenced by the report of McCourt et al. in 1994 (J. Biol Chem. 269:30081-30084) that they had purified this protein and identified it as ICAM-1, a known protein. We had not believed this for several reasons and continued our efforts to purify the authentic liver sinusoidal enothelial cell HA receptor. A subsequent report by McCourt et al. (Int. J. Biochem. Cell. Biol. 29:1179-1189 (1997)) three years later confirmed that ICAM-1 was not, in fact, the liver HA receptor. One reason for the difficulties encountered by this group was that they had no method by which to assay and quantify the activity of this HA receptor during various purification steps.

One nonobvious discovery that we made was that a ligand-blot assay using radioiodinated-HA (described in Yannariello-Brown et al. 1997) enabled us to assay the HA-binding activity of the HA receptor and thus monitor its presence during purification. Nonetheless, by mid 1997 we realized that our biochemical purification strategy would not work and we abandoned it. We then changed our approach completely and developed monoclonal antibodies to the receptor. These unique antibody reagents and the novel ligand-blot assay ultimately enabled us to purify and characterize the liver HA receptor, now designated as HARE.

6. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

2-12-03
Date

Paul H. Weigel
Paul H. Weigel, Ph.D.